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Thrombocytopenia in HIV-Infected and Uninfected Hemophiliacs

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To determine the incidence and prognostic significance of thrombocytopenia among hemophiliacs, we analyzed clinical and hematologic data from the Multicenter Hemophilia Cohort study. Nineteen percent of HIV-infected subjects had thrombocytopenia (platelet count of <100,000/mm^3) noted at least once, compared to 3% of HIV-uninfected subjects. For HIV-infected subjects, the prevalence of thrombocytopenia rose in the first 5 years after seroconversion and was twice as common in subjects age >35 years compared to younger subjects. The risk increased after an AIDS-defining illness, particularly among older subjects, nearly one-half of whom had thrombocytopenia within 1 year after AIDS. When adjusted for age and CD4-positive lymphocyte counts, thrombocytopenia was associated with an increased risk of death [relative risk (RR) 1.7, 95%CI = 1.2–2.3] but with little change in the risk of progression to AIDS (RR = 1.2, 95%CI = 0.8–1.7). Treatment with zidovudine was associated with a decreased risk of thrombocytopenia (RR = 0.5, 95%CI = 0.3–0.7). Although 59 HIV-infected subjects died of hemorrhage, only 11 (19%) of the 59 had a reported platelet count of <50,000/mm^3, and only 2 (3%) of the deaths were temporally associated with thrombocytopenia. Thus, the risk of death was increased for thrombocytopenic HIV-infected hemophiliacs but this was not explained by an increased risk of developing AIDS and was rarely associated with death from bleeding. Am. J. Hematol. 54:296–300, 1997.

Key Words: hemophiliacs; thrombocytopenia; HIV infection; survival

INTRODUCTION

Thrombocytopenia has been reported to occur in approximately 10% of subjects with asymptomatic human immunodeficiency virus (HIV) infection [1] and in 30% of those who have progressed to clinical acquired immunodeficiency syndrome (AIDS) [2]. The longer subjects are HIV infected, the more likely they are to become thrombocytopenic. Subjects in whom thrombocytopenia is detected have fewer CD4-positive lymphocytes [3] and an accelerated decrease in the number of these cells [4]. Thrombocytopenia has been shown to predict progression to AIDS in some cohort studies [5,6] but not in others [7,8].

Among hemophiliacs, thrombocytopenia may place subjects at particularly high risk of bleeding because of their inherited coagulation factor deficiency. It is not known whether thrombocytopenia is more or less common in hemophiliacs than in HIV-infected subjects from other risk groups, nor is it known whether the presence of thrombocytopenia predicts a shorter survival for HIV-infected hemophiliacs.

We analyzed data from a large multicenter cohort of hemophiliacs followed prospectively to determine the prevalence and the prognostic significance of thrombocytopenia in HIV-seropositive and -seronegative hemophiliacs.

METHODS

Data from 961 HIV-infected and 580 HIV-uninfected subjects participating in the Multicenter Hemophilia Cohort Study were analyzed for this study. These were sub-

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jects with congenital coagulation disorders enrolled with informed consent between 1982 and 1985 from eight comprehensive hemophilia treatment centers in the United States. Four additional centers from the United States and four centers from Europe joined the study between 1987 and 1990. At each annual or semiannual visit, blood was obtained, a physical examination performed, and information about clinical status recorded. Causes of death were determined by treatment center physicians. AIDS was defined by the 1987 definition of the Centers for Disease Control (CDC). Splenomegaly was defined as a palpable spleen.

Platelet counts were performed at each center when subjects were seen on a routine basis. For this report, thrombocytopenia was defined as any one platelet count of <100,000/mm^3. The prevalence of thrombocytopenia for a given year was calculated as the fraction of patients with one or more platelet counts of <100,000/mm^3 among all patients with platelet counts during that year. For some analyses, a platelet count of <50,000/mm^3 or<20,000/mm^3 was used to define severe thrombocytopenia.

Coded aliquots of frozen sera obtained from as early as 1976 were tested for antibodies to HIV-1 by commercial enzyme immunoassay, and positive tests were confirmed by immunoblotting. Dates of HIV infection were estimated as the midpoint in time between the last negative and first positive sample for subjects who had such specimens available. For subjects without an HIV-negative serum sample, the date of infection was estimated as the mid-date between July 1, 1978 and the date of the first positive blood sample.

CD4-positive lymphocyte counts were performed annually or semiannually at each center or at a central laboratory by flow cytometry, using commercially available reagents.

Questionnaires were sent to the treatment center physicians, who were asked to classify thrombocytopenia into one of three groups: autoimmune thrombocytopenia, thrombocytopenia due to liver disease, or thrombocytopenia due to HIV infection. The criteria for inclusion in the autoimmune group included the presence of severe thrombocytopenia (platelet count of <25,000/mm^3), increased number of megakaryocytes on bone marrow aspiration and biopsy, presence of antiplatelet antibodies, or responses to immunomodulatory therapy, such as intravenous gammaglobulin or corticosteroids. Criteria for thrombocytopenia attributed to liver disease were thrombocytopenia in the presence of jaundice, elevated liver enzymes, splenomegaly, esophageal varices, or hepatic encephalopathy. Criteria for thrombocytopenia attributed primarily to HIV infection included improvement in thrombocytopenia with institution of zidovudine therapy, coexistent cytopenias, and no other apparent cause for thrombocytopenia. Data for platelet transfusions were not collected.

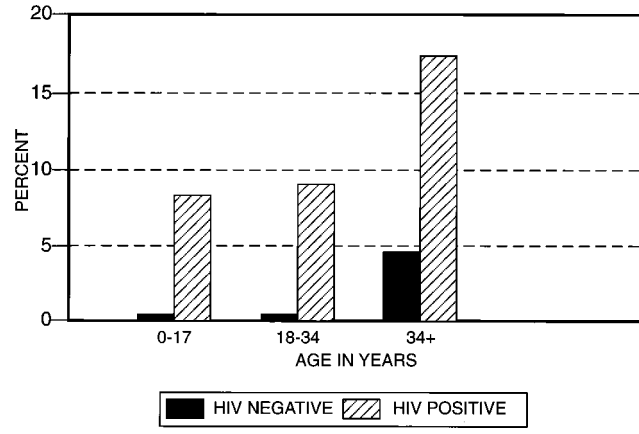

Fig. 1. Mean annual prevalence of thrombocytopenia in 961 HIV- infected and 580 HIV-uninfected hemophiliacs, divided into three groups, 0–17, 18–34 and >34 years of age at seroconversion (or age as of October 1982, for HIV-uninfected subjects).

Statistical analysis was performed using Cox proportional hazard models with time-dependent covariates, which were adjusted for age at seroconversion and in most instances for CD4 count. Relative risk was estimated from the model parameter (β) as e^{β}. Ninety-five percent confidence intervals (CI) were calculated as $e^{\beta \pm 1.96SE(\beta)}$. The likelihood ratio test was used for determining statistically significant differences between groups.

RESULTS

Thrombocytopenia was much more prevalent in HIV-infected hemophiliacs than in uninfected subjects, regardless of their age at seroconversion. One hundred eighty-five of 961 HIV-infected and 16 of 580 HIV-uninfected subjects had thrombocytopenia noted at least once. The mean annual prevalence rates in HIV-infected hemophiliacs were 8.2%, 8.8%, and 17.3% in subjects who seroconverted at ages 0–17, 18–34, and >35, respectively. By contrast, uninfected hemophiliacs in the same age groups had mean annual prevalence rates of 0.3%, 0.3%, and 4.4%, respectively (P <0.0001) (Fig. 1). For the HIV-infected subjects, the prevalence of thrombocytopenia increased over the first 3–5 years after seroconversion, and was then relatively constant, with the oldest group continuing to have the highest prevalence of thrombocytopenia (Fig. 2).

Subjects treated with zidovudine at any time had a substantially lower risk (RR = 0.5, 95%CI = 0.3–0.7) (Table I) of thrombocytopenia, while subjects taking didanosine had a 0.8 relative risk of thrombocytopenia (95%CI = 0.4–2.0). Those treated with trimethoprim-

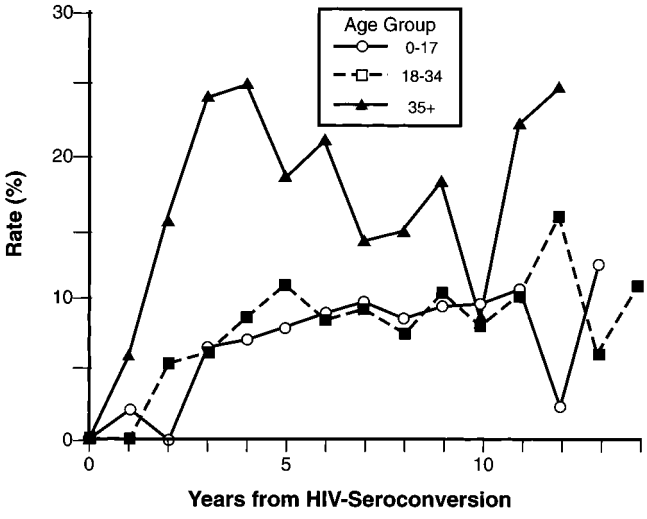

Fig. 2. Prevalence of thrombocytopenia in HIV-infected hemophiliacs as a function of time from seroconversion, separated into groups 0–17 (n = 388), 18–34 (n = 422) and >34 (n = 151) years of age at seroconversion.

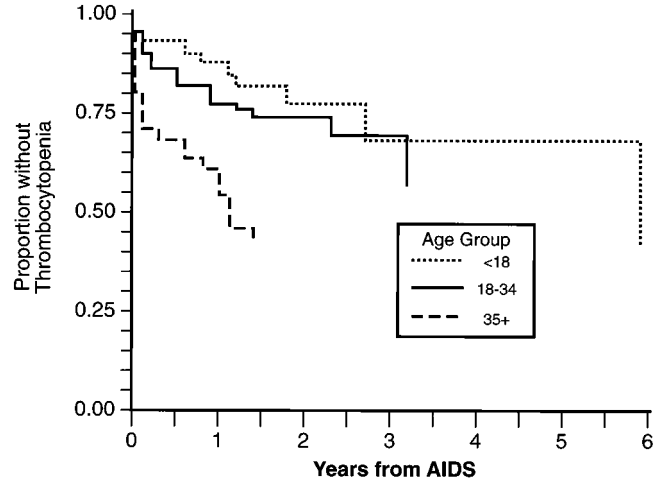

Fig. 3. Proportion of HIV-infected subjects without thrombocytopenia as a function of time from AIDS diagnosis. Three age groups are shown: <18 (n = 73), 18–34 (n = 108), and >34 (n = 58) years of age at seroconversion.

TABLE I. Relative Risk of Thrombocytopenia Among HIV-Infected Persons With Hemophilia

Condition	No. with condition	Relative risk of thrombocytopenia	95% CI
Any zidovudine therapy	639	0.5	(0.3–0.7)
Any didanosine therapy	222	0.8	(0.4–2.0)
Any trimethoprim—sulfamethoxazole therapy	305	1.0	(0.5–1.8)
Splenomegaly	418	1.5	(1.1–2.1)

TABLE II. Relative Risk for AIDS Among HIV-Infected Hemophiliacs

Condition	Relative risk of progression to AIDS	95% CI
Thrombocytopenia, unadjusted for CD4	1.9	(1.3–2.6)
Thrombocytopenia, adjusted for CD4	1.2	(0.8–1.7)
Immune mediated thrombocytopenia	0.8	(0.3–2.6)
Any thrombocytopenia except immune mediated	1.2	(0.8–1.7)

sulfamethoxazole had a 1.0 relative risk of having thrombocytopenia (95%CI = 0.5–1.8), and those with splenomegaly at any time had a relative risk of thrombocytopenia of 1.5 (95%CI = 1.1–2.1).

The risk of becoming thrombocytopenic increased markedly after an AIDS-defining illness, particularly for those older than 35 years at seroconversion (Fig. 3). For this age group, the risk of developing thrombocytopenia within 1 year after an AIDS-defining illness was 50% ($P \leq 0.01$ versus subjects age <18 years or 18–34 years at seroconversion).

Thrombocytopenia (<100,000/mm^3) increased the relative risk of progression to AIDS in unadjusted analyses, but when adjusted for CD4 counts the relative risk of progression was only 1.2 (95%CI = 0.8–1.7) (Table II). More severe thrombocytopenia did not increase the predictive value of thrombocytopenia for AIDS with relative risks of 0.9 (95%CI = 0.4–1.8) and 2.3 (95%CI = 0.7–7.3) for platelet counts of <50,000 and <20,000, respectively.

Thrombocytopenia was associated with an increased risk of death, whether thrombocytopenia was defined as platelet counts of <100,000/mm^3 (RR = 1.7, 95%CI = 1.2–2.3), <50,000 (RR = 1.7, 95%CI = 1.2–2.3), or <20,000 (RR = 2.2, 95%CI = 0.8–6.1) (Table III). The increased risk of death was similar, whether the thrombocytopenia was detected before an AIDS diagnosis (RR = 1.6, 95%CI = 1.0–2.4) or after an AIDS-defining illness (RR = 1.5, 95%CI = 0.9–2.3).

Of the 961 HIV-infected subjects, hemorrhage was listed as the primary or contributory cause of death for 59 subjects. Eleven of these 59 decedents had at least one platelet count of <50,000/mm^3. One decedent had a platelet count of 13,000/mm^3 within 2 days of death, and another had a platelet count of 36,000/mm^3 detected on the day he died from liver disease with variceal hemorrhage. The other nine decedents had platelet counts of <50,000/mm^3, at 7–132 (median 11) months before death.

Among the 580 subjects who were not HIV infected, 10 died of hemorrhage, but none of these subjects had any platelet counts of <50,000/mm^3.

The cause of thrombocytopenia could be characterized

TABLE III. Relative Risk of Death Among HIV-Infected Persons With Hemophilia

Condition	Relative risk of death*	95% CI
Thrombocytopenia, unadjusted for CD4	2.4	(1.7–3.3)
Thrombocytopenia, adjusted for CD4	1.7	(1.2–2.3)
$<100{,}000/mm^3$	1.7	(1.2–2.3)
$<50{,}000/mm^3$	1.7	(1.0–2.8)
$<20{,}000/mm^3$	2.2	(0.8–6.1)
Thrombocytopenia before AIDS diagnosis	1.6	(1.0–2.4)
Thrombocytopenia after AIDS diagnosis	1.5	(0.9–2.3)

*Relative risk of death was age-adjusted.

clinically for 70 (38%) of the HIV-infected subjects. The other 115 HIV-infected subjects with thrombocytopenia did not fit into an a priori category or were thought to have more than one cause of thrombocytopenia. The median age of subjects with thrombocytopenia attributed to liver disease was 42 years compared to 18 years for those subjects with autoimmune thrombocytopenia and 26 years for those with thrombocytopenia attributed to HIV. Compared to subjects with thrombocytopenia attributed to autoimmune mechanisms or liver disease, the subjects with thrombocytopenia attributed to HIV infection had a lower median CD4 count when thrombocytopenia was diagnosed, a longer time from seroconversion to thrombocytopenia and shorter times from the diagnosis of thrombocytopenia to a diagnosis of AIDS or to death (Table IV).

DISCUSSION

We have shown that HIV-infected hemophilic subjects are much more likely to be thrombocytopenic than HIV-uninfected hemophiliacs. This may reflect the increased incidence of thrombocytopenia described in other groups who are HIV-infected, in addition to the risk of thrombocytopenia from other hemophilia-associated disorders such as liver disease attributed to hepatitis C virus (HCV). In subjects with hemophilic liver disease who have progressed to cirrhosis, splenomegaly may also contribute to the thrombocytopenia.

Older hemophiliacs in general, and particularly older HIV-infected hemophiliacs, were more frequently thrombocytopenic than were younger subjects. This may be due to more advanced liver disease producing cirrhosis, portal hypertension and splenomegaly with resultant thrombocytopenia. Increased sensitivity to medications in older subjects also might contribute to the increased prevalence of thrombocytopenia in this group, although we found that thrombocytopenia was not associated with trimethoprim-sulfamethoxazole therapy commonly used for HIV-infected subjects. The use of zidovudine was associated with a lower risk of thrombocytopenia, confirming the effect that this drug has on ameliorating thrombocytopenia in HIV-infected subjects in general [9].

The prevalence of thrombocytopenia increased most during the first 3–5 years of infection with HIV. Thus, thrombocytopenia was not due to acute HIV infection. This increasing prevalence early in the course of HIV infection may represent early immune dysregulation with autoimmune destruction of platelets.

A platelet count of $<100{,}000/mm^3$ at any point during the course of HIV infection in a hemophilic subject was associated with a risk of death 1.7 times that of a non-thrombocytopenic hemophilic subject. This effect is likely distinct from the established association between platelet counts and CD4 lymphocyte counts [3], since in our study, CD4 lymphocyte counts were controlled as time-dependent covariates in all analyses. Similarly, this effect should not be due to the increased prevalence of thrombocytopenia with increasing age, since these analyses were corrected for age at seroconversion. However, we cannot exclude residual confounding as an explanation for our findings. We expected thrombocytopenia to increase the likelihood of death from bleeding in our cohort of 1,541 subjects who have an inherited coagulation disorder. While we demonstrated that thrombocytopenia was associated with an increased risk of overall mortality for HIV-infected hemophiliacs, there were no clear temporal associations between fatal bleeding and platelet counts of $<50{,}000/mm^3$. Likewise, none of 10 HIV-uninfected subjects who died of hemorrhage had any platelet count of $<50{,}000/mm^3$ reported. This was surprising, as hemorrhage is second only to AIDS as the most common cause of death for the HIV-infected subjects in this cohort [10] and in other cohorts of hemophilic patients [11]. It must be noted, however, that our study addressed only mortality and did not assess morbidity due to hemorrhage. Furthermore, only platelet counts reported on study forms were included in this analysis, and data on platelet transfusions were not available. Therefore, cautious management of hemophiliacs with platelet counts of $<50{,}000/mm^3$ is still appropriate [12].

Although most of the deaths in the HIV-infected hemophiliacs were from AIDS, thrombocytopenia was associated with an increased the risk of death, but not of AIDS. In part, this is because thrombocytopenia may occur after AIDS, especially in older subjects. In addition to this obvious explanation, thrombocytopenia may be a surrogate marker for a condition other than AIDS that accelerates progression to death such as hemophilic liver disease due to chronic HCV infection. Chronic HCV is present in the vast majority of multitransfused hemophiliacs, worsens with age, and causes cirrhosis in at least 20% of those with long-standing infection [13]. Coinfec-

TABLE IV. Selected Clinical Characteristics of HIV-Infected Hemophiliacs With Autoimmune, Liver Disease or HIV-Associated Thrombocytopenia

Type	(N)	Age at TP* (yr)**	CD4 count at TP (cells/mm^3)	Time from seroconversion to TP (yr)	Time from TP to AIDS (yr)	Time from TP to death (yr)
Autoimmune	26	18 (6–55)	459 (0–1278)	4.1 (0.6–8.2)	2.7 (1.6–9.1)	4.2 (1.7–4.7)
Liver disease	16	42 (16–65)	511 (97–880)	4.0 (−3.2–8.6)	3.1 (2.2–3.5)	4.5 (1.25–9.2)
HIV infection	28	26 (6–65)	272 (39–899)	5.2 (<1–9.2)	2.4 (0.4–3.1)	2.7 (0.3–3.9)

*Thrombocytopenia.
**All values are medians (range).

tion with HCV and HIV has been shown to accelerate the course of HCV liver disease [13].

The high prevalence of thrombocytopenia after an AIDS-defining illness, especially in the older age group, probably represents a combination of severe illness and the toxicities of the many medicines with which these subjects are treated. Because this group constituted only a small proportion of the cohort, it did not appreciably influence our finding that the prevalence of thrombocytopenia in the cohort increases until about the fifth year from seroconversion, and then levels off.

Etiologic classification of thrombocytopenia was difficult. For most subjects, the cause of the thrombocytopenia was not apparent, or there were multiple causes without a predominant cause. This was especially common as subjects became increasingly ill. Although we were able to assign a cause of thrombocytopenia in only 38% of cases, we believe it remains important to try to determine the cause of thrombocytopenia, since this would influence therapy.

In summary, we have shown that while thrombocytopenia is associated with an increased risk of death, it is rarely temporally associated with death from bleeding. We suspect that thrombocytopenia may act as a surrogate marker for other illnesses that prove fatal to these hemophilic subjects, perhaps hemophilic liver disease. It may only be through analysis of other groups of patients, who lack the complicating features of hemophilia and the chronic liver disease common to these patients, that the precise relationship between thrombocytopenia and increased risk of death can be determined.

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